REMARKS

Attached hereto is a marked up version of the changes made to the claims by this amendment. The attachment is captioned "**Version With Markings to Show Changes Made.**"

In response to the objections raised by the Examiner in the September 25, 2001 Office Action, our comments follow. Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 12 and 13 have been amended. Support for the amended claims can be found throughout the specification and particularly on page 14, lines 27-29. Claims 51-54 have been added. Claims 51 and 53 correspond to claims 1 and 13, but specify the corresponding sequence as being selected from the sequences of the polypeptides recited on pages 15 to 22 of the application as having "clear homology" to the apical domain (residues 191-375). Claims 52 and 54 correspond to claims 1 and 13, but specify the corresponding sequence as being a corresponding sequence of a chaperone selected from the group listed in Figure 9. Claims 1, 9-21, 29-31 and 51-54 are now pending. No new matter is added by these amendments.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support is found throughout the specification and from the pending claims.

II. THE REJECTION UNDER 35 USC §112, FIRST PARAGRAPH, IS OVERCOME

Claim 1 was rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. The rejection is traversed.

Claim 1 has been amended to define the homology of the "corresponding sequences" as sharing at least 50% homology with the amino acid selected sequence. References to "modified, mutated or variant" sequences have been removed. As described on page 7, lines 13 to 18 of the

specification, a problem which the present invention seeks to solve is the provision of an active portion or fragment of a chaperone in truly monomeric form to promote a useful reagent for refolding. A further problem is the provision of such a monomeric form at minimal size. These obstacles have been overcome by the provision of the chaperone polypeptide as claimed in claim 1. The description (see, for example page 58) discloses that residues 230–271 are in the binding site of GroEL and that fragments having this region have refolding activity (see, for example, Examples 2, 3, 4, 10 and 11). Thus, the specification clearly teaches that the presence of such residues confers the required refolding activity on GroEL fragments.

Moreover, the specification teaches that the equivalent residues of substantially homologous regions are included within the scope of the invention. Page 15, line 5 discloses that many chaperone polypeptides, for example of the Hsp60 class, are generally homologous in structure. An extensive list of numerous Hsp60 chaperones with the required homology to the apical region of GroEL is recited on pages 15 to 22. Moreover, the sequence alignment of Hsp60 family members with GroEL, described in Example 12 and shown in Figures 9a–9e, shows consensus in residues 230-270. Thus, the specification clearly teaches that there is strong homology between the 230-271 fragment of GroEL and corresponding fragments of other chaperones that may be used.

Therefore, it is submitted that the specification clearly discloses common identifying characteristics of the chaperones of the invention (the presence of residues 230-271 of the GroEL chaperone or the corresponding sequence of related chaperones). It is clear that the inventors had possession of the invention at the time the application was filed and that the specification is sufficient to put one of skill in the art in possession of the attributes of all species of chaperone as claimed.

Thus, it is respectfully submitted that the assertion in the Office Action that claim 1 contains subject matter not adequately described in the specification is obviated. Consequently, the Section 112, first paragraph, rejection should be reconsidered and withdrawn; such relief is respectfully requested.

III. THE REJECTION UNDER §112, SECOND PARAGRAPH, IS OVERCOME

Claims 1, 9-11, 14-21 and 29-31 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The terms "substantially homologous" and "modified, mutant or

variant" have been deleted from claim 1. Consequently, reconsideration and withdrawal of the rejection is believed to be in order and such action is respectfully requested.

IV. THE REJECTION UNDER §102 IS OVERCOME

Claims 1 and 9-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Braig *et al.* This rejection is respectfully traversed.

The Applicants admit that Braig *et al.* disclose the amino acid sequence of *E.coli* GroEL. Indeed, this is taught on page 2, lines 16-17, of the present application. However, the sequence disclosed by Braig *et al.* is the entire sequence and not a fragment thereof. There is no teaching of any fragments, let alone of any of the particular fragments claimed in the present application. Thus, it is submitted that the Office Action's assertion that Braig *et al.* disclose such fragments is incorrect.

Moreover, even if it could be argued that Braig *et al.* did indeed suggest that fragments of the recited sequence could be made, which, of course, we do not admit, the fragments produced would not anticipate the chaperone polypeptide as claimed in the present application. As described in the specification on page 7, line 26, to page 8, line 3, fragments of the GroEL sequence in which positions 262 and 267 are occupied by alanine and isoleucine, respectively, are inoperative and unable to promote folding of polypeptides. Therefore, a fragment of the polypeptide disclosed by Braig *et al.* in which positions 262 and 267 are occupied by alanine and isoleucine, respectively, would not demonstrate "chaperone activity" as defined in the specification on page 8, lines 23 to 28, and thus could not be defined as a "chaperone polypeptide", as required by the claims.

For these reasons, reconsideration and withdrawal of the Section 102 rejection is believed to be in order and such action is respectfully requested.

V. THE REJECTION UNDER §103 IS OVERCOME

Claims 1, 9-21 and 29-31 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Braig *et al.*, in view of Holland *et al.* A person skilled in the art would not have been motivated to make a recombinant *E. coli* GroEL fusion polypeptide in view of these citations, as these citations actually teach away from the present invention. Braig *et al.* and Holland *et al.* do not teach or suggest fragments of *E. coli* GroEL polypeptides that have chaperone activity as described on page 7, lines 9 to 24 of the present application and as in the claims.

Braig *et al.* neither teach that fragments of the GroEL sequence disclosed therein may be made and may have chaperone activity, nor do they teach that fusion polypeptides may be made. Holland *et al.* teach a process of making recombinant fusion polypeptides, but do not teach the use of GroEL polypeptides or fragments thereof. Thus, even if the skilled person was motivated to make a GroEL fusion polypeptide in view of Braig *et al.* and Holland *et al.*, neither document provides any incentive or suggestion to the skilled person to utilize the fragments of GroEL as taught in the present application. Moreover, even if the skilled person was to make a fusion polypeptide using fragments based on the sequence disclosed in Braig *et al.*, the fragment, and thus the fusion polypeptide, would not, for the reasons given above, have chaperone activity.

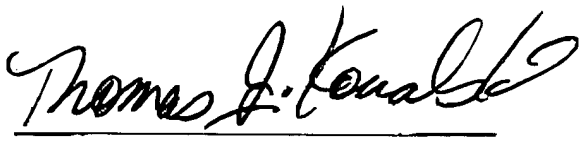
Accordingly, Claims 1, 9-21 and 29-31 do not lack inventive step. Reconsideration and withdrawal of the Section 103 rejection is believed to be in order and such action is respectfully requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicant



Thomas J. Kowalski
Reg. No. 32,147
Tel: (212) 588-0800

Version with Markings to Show Changes Made

IN THE CLAIMS

1. (Twice Amended) A chaperone polypeptide having an amino acid sequence selected from at least amino acid residues 230-271 but no more than residues 150-455 or 151-456 of a GroEL sequence as shown in Figure 7, or a corresponding sequence of a [substantially homologous] chaperone polypeptide, said corresponding sequence sharing at least 50% homology with said amino acid sequence[or a modified, mutated or variant sequence thereof having chaperone activity].

12. (Twice Amended) A polypeptide as claimed in claim 1 which comprises at least an amino acid sequence selected from GroEL residues:

(a) 191-329, 191-330, 191-331, 191-332, 191-333, 191-334, 191-335, 191-336, 191-337, 191-338, 191-339, 191-340, 191-341, 191-342, 191-343, 191-344, 191-345, 191-346, 191-347, 191-348, 191-349, 191-350, 191-351, 191-352, 191-353, 191-354, 191-355, 191-356, 191-357, 191-358, 191-359, 191-360, 191-361, 191-362, 191-363, 191-364, 191-365, 191-366, 191-367, 191-368, 191-369, 191-370, 191-371, 191-372, 191-373, 191-374, 191-375 or 191-376, or

(b) 192-329, 192-330, 192-331, 192-332, 192-333, 192-334, 192-335, 192-336, 192-337, 192-338, 192-339, 192-340, 192-341, 192-342, 192-343, 192-344, 192-345, 192-346, 192-347, 192-348, 192-349, 192-350, 192-351, 192-352, 192-353, 192-354, 192-355, 192-356, 192-357, 192-358, 192-359, 192-360, 192-361, 192-362, 192-363, 192-364, 192-365, 192-366, 192-367, 192-368, 192-369, 192-370, 192-371, 192-372, 192-373, 192-374, 192-375 or 192-376, or

(c) 193-329, 193-330, 193-331, 193-332, 193-333, 193-334, 193-335, 193-336, 193-337, 193-338, 193-339, 193-340, 193-341, 193-342, 193-343, 193-344, 193-345, 193-346, 193-347, 193-348, 193-349, 193-350, 193-351, 193-352, 193-353, 193-354, 193-355, 193-356, 193-357, 193-358, 193-359, 193-360, 193-361, 193-362, 193-363, 193-364, 193-365, 193-366, 193-367, 193-368, 193-369, 193-370, 193-371, 193-372, 193-373, 193-374, 193-375 or 193-376, or

(d) 230-271, 229-271, 229-272, 228-272, 228-273, ...*et seq*... 194-328, 194-329, or

[the equivalent residues of substantially homologous chaperonins, or a modified, mutated or variant sequence thereof] a corresponding sequence of a chaperone polypeptide, said corresponding sequence sharing at least 50% homology with said amino acid sequence.

13. (Amended) A monomeric polypeptide, having chaperone activity and incapable of multimerisation, characterised in that, in the absence of ATP, the polypeptide has a protein refolding activity of more than 50%, said refolding activity being determined by contacting the polypeptide with an inactivated protein of known specific activity prior to inactivation, and then determining the specific activity of the said protein after contact with the polypeptide, the % refolding activity being:

$$\frac{\text{specific activity of protein after contact with polypeptide}}{\text{specific activity of protein prior to inactivation}} \times \frac{100}{1}$$

wherein the selected amino acid sequence is selected from the group consisting of 230-271, 191-345, 191-376, 193-335 and 193-337 of GroEL, or a corresponding sequence of a chaperone polypeptide, said corresponding sequence sharing at least 50% homology with said amino acid sequence[the equivalent residues of substantially homologous chaperonins, and a modified, mutated or variant sequence thereof].